REMARKS

Claims 90-93, 96-101, 104 and 133-151 were previously pending in this application. By this amendment Applicants are canceling claims 91-92, 97, and 147-148 without prejudice or disclaimer. Claims 98, 104 and 133 have been amended. No new matter has been added.

Support for the amendments to claim 104 is found in now cancelled claims 91 and 97, the limitations of which have been incorporated into claim 104, as well as the specification at least on page 19 lines 1-8 and parent application (incorporated by reference) US 08/386,063 now US 6,194,308 in column 7 line 66-column 8 line 12. Claim 98 was amended to change the dependency from now canceled claim 97 to claim 104. Claim 133 was amended to clarify the term "terminal."

As a result, claims 90, 93, 96, 98-101, 104, 133-146, and 149-151 are pending for examination with claim 104 being an independent claim.

Under the status of the claims and in each of the rejections the Examiner has listed the pending claims as 90-93, 96-101, 105 and 133-151. Applicants believe that the Examiner meant to list the claims as 90-93, 96-101, 104 and 133-151 since claim 104 is pending and 105 is canceled. Therefore, throughout the rest of the document Applicants replace claim 105 with 104 when referring to the Examiner's rejections.

Information Disclosure Statement

The Examiner has rejected 5 Information Disclosure Statements (IDSs) as not complying with 37 CFR 1.56. The Examiner has sampled the references and did not find any reference that teaches the claimed invention or makes the claimed invention obvious. Applicants agree that the invention is novel and non-obvious. However, Applicants traverse the objection to the IDS for the reasons set forth below.

37 CFR 1.56 requires each individual associated with the filing to disclose to the Office all information known to that individual to be material to patentability. Applicants have provided references that one of ordinary skill in the art may consider to be material to

patentability therefore complying with 37 CFR 1.56. Applicants cannot make the Examiner's rejections for her. Applicants do not know which combinations of references the Examiner might cite. If Applicants did not submit the information to the patent office it might be considered to be fraud. As a result Applicants will continue to submit the information in the form of IDSs. However, without conceding to the Examiner's position and solely in the interest of expediting prosecution, a new IDS will be submitted.

Rejections under 35 U.S.C. § 112

Definiteness

The Examiner has rejected claims 90-93, 96-101, 104 and 133-151 under 35 U.S.C. § 112, second paragraph, as being indefinite.

Claim 104 has been rejected because of the term "stabilized". Although the term is defined in the specification, Applicants have amended claim 104 to incorporate the limitation of now canceled claim 91 and removed the term "stabilized".

Claims 134-135 are rejected because the values of X_1-X_4 are not defined. It is believed that the rejection is moot in view of Applicants amendments to the claims to incorporate the limitations of former claim 97.

Claim 133 has been amended to clarify that the term "terminal" refers to the terminal end of the oligonucleotide.

Written Description

The Examiner rejected claims 133, 135, 137 and 139 under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. Claim 133 has been rejected for a lack of written description support for the term "GCG trinucleotide." Support for the term is found in parent application (incorporated by reference) US 08/386,063 now US 6,194,308 at least in column 8 line 10-12.

Enablement

The Examiner rejected claims 90-93, 96-101, 104 and 133-151 under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement. According to the Examiner, the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. The Examiner has presented a rejection based on the Wands factors. Each of the specific rejections is addressed separately by Applicants below.

Nature of the invention

The invention is directed to a method of treating bacterial infection using a class of CpG containing oligonucleotides having structural requirements such as a phosphate backbone modification.

Breadth of the Claims

The claims broadly cover the treatment of bacterial infection using CpG oligonucleotides. The amended claims do contain several structural limitations on the CpG oligonucleotide. The CpG must include an unmethylated CpG flanked on each side by at least two other nucleotides. The oligonucleotide also includes a phosphate backbone modification.

State of the Art

The Examiner has made several statements about the state of the art. In order to address each statement, Applicants have copied the Examiner's statement and provide comments immediately below.

- Cytokines have great potential for enhancing resistance against diverse pathogens; however, host response to exogenously administered cytokines can be dichotomous and may be dependent on the pathogenesis caused by the disease state. (Office Action page 8)

- The statement is not relevant to the claimed invention. Applicants are not exogenously administering cytokines. The claimed invention relates to the delivery of an oligonucleotide which stimulates in vivo the promotion or inhibition of cytokine production.

- Both Th1 and Th2 type of immune responses is necessary. Infante-Duarte et al. notes that it is important to produce enough of the Th1 type immune response to keep intracellular infection under control, while producing at the same time just enough of a Th2 type immune response to prevent the Th1 type immune response from causing damage to the host. In order to do so, a tight control over where and when Th1 and Th2 immune responses happen is necessary. (Office Action page 9)
  - This teaching is not inconsistent with the claimed invention. The patent application teaches that CpG oligonucleotides promote an immune response when administered in vivo. The immune response involves a shift in the balance of Th1 and Th2 cytokines such that the Th1 response is favored. The shift is a natural one that occurs in response to a stimulus that Applicants believe a naturally existing stimulant, bacterial DNA. It is believed that CpG containing oligonucleotides mimic bacterial DNA in their ability to promote an immune response. The inventors believed they discovered one of natures pathways fundamental to the immune system. This discovery is described on pages 35-36 of the specification under the heading "Teleological Basis of Immunostimulatory Nucleic Acids." It is taught that the stimulatory CpG motif, identified according to the invention, is common in microbial genomic DNA, but quite rare in vertebrate DNA. Experiments described in Example 3, in which methylation of bacterial DNA with CpG methylase was found to abolish mitogenicity, demonstrated that the difference in CpG status is the cause of immune stimulation by bacterial DNA. The resultant immune response is a natural one. Not one that is dramatically skewed to cause tissue damage.

- The efficacy of cytokines such as interleukin 2, interferon-gamma, and interleukin 18, remains controversial. For example, while interleukin 2 may confer good protection for non-pathogenic mycobacterial strain Bacille Calmette-Guerin (BCG), interleukin 2 does not confer protection for virulent *M. bovis* infection. (Office Action page 9)
    - The statement is not relevant to the claimed invention. Applicants are not directly administering a cytokine. Additionally, the claimed invention relates to the delivery of an oligonucleotide which stimulates a pattern of cytokine production, not simply a single cytokine, such as IL-, IFN, or IL-18. Additionally, the Aoki et al reference cited by the examiner actually teaches that cytokines have promise in the treatment of infectious disease. On page 231 2nd column it is concluded that "Undoubtedly, in the next several years we may witness the formal introduction of cytokines or their inhibitors to routine clinical use for infectious diseases other than viral hepatitis." and "Cytokines hold great promise to be used as therapeutics or immune adjuvant for vaccination against infectious disease.....Several cytokines have been successfully used for human conditions and it is anticipated that more will enter into clinical applications."
- Interleukin-12, Th1 associated cytokine, induces different effector mechanisms that result in either protection or exacerbation. Bohn et al. teaches that the administration of exogenous interleukin 12 confers protection against Yersinia enterocolitica in susceptible BALB/c mice, but exacerbates yersiniosis in resistant C57BL/6 mice. (Office Action page 9)
    - Again, the statement is not relevant to the claimed invention. Applicants are not directly administering a cytokine. Additionally, the claimed invention relates to the delivery of an oligonucleotide which stimulates a pattern of cytokine production, not simply a single cytokine such as IL-12.

- Interleukin 18, a Th1 associated cytokine, is responsible for the progression of endotoxin-induced liver injury in mice primed with interleukin 18. (Office Action page 10)
    - The statement is not relevant to the claimed invention. Applicants are not directly administering IL18. Administering a compound is very different than stimulating the body to produce the compound endogenously.
- Interleukin 6 and interferon gamma, both are Th1 associated cytokines, augment the susceptibility of monocyte-derived macrophages to infection with T-cell tropic CXCR4-utilitising HIV-1 strains; whereas, IFN-gamma inhibits viral entry and productive infection of mono-derived macrophages with macrophage-tropic HIV-1. (Office Action page 10)
    - The statement is not relevant to the claimed invention. HIV is a virus. Applicants claims are limited to the treatment of bacterial infection.
- Interleukin 2, a Th1 associated cytokine, increases the production of HIV in vitro, and enhances the translocation of bacteria from intestines to other organs in animal studies. Additionally, the art also notes that a higher incidence of bacterial infections in AIDS patients receiving IL-2 treatment. (Office Action page 10, citing Masihi)
    - The statement is not relevant to the claimed invention. Applicants are not directly administering a cytokine. Administering a compound is very different than stimulating the body to produce the compound endogenously. This point is clarified in the Masihi reference itself. In his review article Masihi describes several classes of molecules and how they are used for fighting infection. One section (section 3) is on the exogenous administration of cytokines as therapeutic agents. This is the section cited by the Examiner which describes some of the troubles associated with exogenous administration of cytokines. The next section (section 4) describes synthetic and natural immunomodulators. Section 4.1 is dedicated

to CpG oligonucleotides. Unlike all of the problems highlighted by Masihi related to cytokines, Masihi describes studies in which CpG ODN were demonstrated to protect against *Listeria moncytogenes* and *Francisella tularensis* in mice. Additionally studies are described relating to successful protection against *Trypansoma Cruzi* and *Leishmania major.* The author even concludes "CpG-ODN were even curative when given after lethal *Leishmania major* infection.: (0age 647 1st full sentence).

- Interferon gamma is ineffective against the virulent strain of Mycobacterium avium. Silva et al. notes that the virulent strain resists the antimycobacterial activity of interferon-gamma. (Office Action page 10)
  - The statement is not relevant to the claimed invention. Applicants are not directly administering a cytokine. Administering a compound is very different than stimulating the body to produce the compound endogenously. Additionally the cited statement from the Silva reference is incorrect. On page 5583 last sentence left column Silva et al actually states that "virulent strains resist the antimycobacterial activity of *IFN-γ-activated macrophages*" (emphasis added.) IFN-γ-activated macrophages are different than IFN-γ.

Based on the above assertions, the Examiner concludes that "the art amply recognizes the following limitations: inherent toxicity of the material, their unclear pharmacological behavior, and their pleiotropic effects." None of the above-statements support the above conclusions. In each instance but one (the one referring to Infante-Duarte et al.) the Examiner is describing a system of one or more exogenously administered cytokines. Applicants have not claimed the administration of cytokines. Applicants claims are directed to the administration of oligonucleotides which produce a shift in the balance of cytokine production and cellular activation in a natural environment. The body controls how much of a particular cytokine to produce. The effect is different from administering cytokines. The ability to stimulate an immune response without directly administering

immune factors such as cytokines is an advantage of the invention. The teachings of Infante-Duarte et al. cited by the Examiner are not inconsistent with the claimed invention and also don't support the above-conclusion.

Additionally, the Examiner has cited several teachings in the CpG art. Applicants addresses each of these below.

- The recognition of the CpG motifs requires Toll-like receptor (TLR) 9, wherein cells that express TLR-9 produce Th1 like proinflammatory cytokines, interferon and chemokines. However, the art also recognizes that TLR-9 is differentially expressed in human mice, and that TLR-9 has not been identified in species other than human and mice. Thus, with the variability of TLR-9 expression, including absence thereof, the level of a Th-1 immune response would also be variable from one species of animals to the next. (Office Action page 11, citing Mutwiri et al)

  Mutwiri et al actually state "TLR9 has yet to be identified in species other than human and mice, *but it is assumed that a similar signaling mechanism is involved in other species*". (Emphasis added) The Examiner's conclusion that the absence of TLR9 in some species would lead to variability in results is misplaced. The reference does not teach that TLR9 is absent is some species. Additionally the reference is a review article describing studies that have examined the effects of CpG therapies in a variety of animals, including mice, humans, cattle, sheep, pigs, horses, goats, rabbits, fish, dogs, cats, and chickens (see for instance page 90 first full paragraph of left column and first 20 lines of right column). The authors conclude in that paragraph in the right column of page 90 that "Together, these data suggest that in vitro stimulation of cells by CpG motifs is conserved across species, and that the enhanced activity of GACGTT in laboratory animals may be an artificial bias due to inbreeding."

- Every oligonucleotide containing the CpG motif must be considered as a separate agent because the quality and type of immune stimulation induced by these oligonucleotides varies. The art frequently notes that the specific nucleic acids, purines and pyrimidines, surrounding the CpG motif, influence both the level and type of immune stimulation; the spacings between CpG motifs surrounding the CpG motif influence both the level and type of immune stimulation; and the type of cytokine stimulated by oligonucleotides containing the CpG motif varies from one oligonucleotide to the next. The art also notes that variability occurs with different numbers of CpG motifs in an oligonucleotide, the absence or presence of a CpG motif to the end of the oligonucleotide, and the context in which the CpG motif is presented in the sequence. (Office Action page 10)

  - Applicants have described a class of molecules (oligonucleotides) having a common structural motif (a CpG dinucleotide) that when administered to a subject results in an aspect of the immune response being altered, with a Th1 response being favored. This class of oligonucleotides is described throughout the specification and their ability to produce a Th1 favored immune response and be used to treat disease is not only described (e.g., see page 8, lines 5-16 and page 40-42) but data is presented *in vitro* and *in vivo* using an adequate number of different CpG containing oligonucleotides to meet the enablement requirement for the claimed invention. The fact that there is some variability in the responses depending on the sequence of the oligonucleotide is not surprising. If one were proceeding in a clinical trial one would have to select a single oligonucleotide to use. However, this is not the standard for enablement. Variability with drugs in humans is not unusual. Humans are an outbred population, genetically diverse, and humans respond with great variability to drugs. This is particularly the case where the immune system is involved. Humans have an immune status that fluctuates much more than the mice used in experimental research. A

human's immune status on any particular day can determine the human's response to a drug.

- In vitro observations do not accurately predict what happens in vivo. (Office Action page 12, citing Mutwiri et al)
  - The cited statement is true for any biological agent. A regulatory authority such as the FDA would not approve a drug simply on the basis of in vitro tests. However, this is not the standard for patentability. The statement is not specific and has no bearing on the enablement of the claims.
- The immunostimulatory activity of CpG oligonucleotides is species specific. The human CpG motif, GTCGTT, is optimal for stimulation of lymphocyte proliferation in several species including cattle, sheep, goats, horses, pigs, dogs, cats and chickens. And the murine CpG motif (GACGTT) is only optimal for inbred rabbits and mice. (Office Action page 12, citing Mutwiri et al)
  - The statement does not provide support for lack of enablement. Simply because one embodiment might be optimal or preferred does not make other embodiments non-enabled. Additionally, the statement taken from Mutwiri et al reflects the analysis of data from several published articles. It does not purport to analyze each and every CpG ODN.
- The immunomodulatory effect induced by oligonucleotides containing the CpG motif varies from one species to another. (Office Action page 12, citing Mutwiri et al)
  - As described above, variability is expected. However, it has been described in the specification and confirmed in numerous references that CpG containing oligonucleotides stimulate an immune response. The consistent effect is attributed to the presence of the unmethylated CpG motif in the oligonucleotide.
- Oligonucleotides containing the CpG motif increase the susceptibility to infection by *Candida albicans*. Ito et al. notes that although oligonucleotides containing

the CpG motif promote Th1 immunity, the induction of IL-12 by the oligonucleotide increases infection by *Candida albicans* in mice, rather that protecting the mice from said infection. (Office Action page 13, citing Ito et al)

- *Candida albicans* is a yeast, not a bacteria. The claimed invention is directed to the treatment of bacterial infection using CpG oligonucleotides. Ito et al states that CpG ODN "treatment typically improves host resistance to infection by bacterial, viral, and parasitic pathogens." (page 6154, left column, first paragraph last sentence)

Thus, none of the references or passages cited by the Examiner support a conclusion of the lack of enablement of the claimed invention.

Presence or absence of working examples:

The Examiner has stated that the "specification does not contain any working examples suggesting or demonstrating that the administration of an oligonucleotide containing the CpG motif is effective in treating bacterial infection....All that is present in the specification are working examples directed at measuring the effect of various structural manipulations of oligonucleotides containing the CpG motif."

Applicants have taught that in addition to induction of IFN-gamma the working examples in the specification show production of antibody in response to oligonucleotide stimulation (Example 2), stimulation of B cells, natural killer (NK) cells and monocytic cells (Example 3, Example 4, Example 11, Figure 6 and Figure 11), and production of IFNγ (Figure 15) as well as other cytokines. The specification asserts that CpG oligonucleotides are useful in treating bacterial infections. The combination of the changes in immune parameters demonstrated with CpG oligonucleotides is sufficient to support applicants assertion at the time of the invention that CpG oligonucleotides would be useful in the treatment of bacterial infection. Applicants assert that a correlation between CpG and their use in the treatment and/or prevention of bacterial infection is disclosed and enabled.

Amount of direction or guidance presented:

Applicants have provided sufficient direction and guidance in the specification. Applicant has described the structural properties of CpG oligonucleotides and have taught that they can be used to treat bacterial infection. Further applicants have provides preferred modes of administration and formulations. Those of skill in the art are well aware of such routine methods of formulating and administering drugs.

Predictability or unpredictability of the art:

The Examiner has stated that "As demonstrated by Applicant in the disclosure and the teachings in the art, the use of oligonucleotides containing CpG motif is unpredictable." Applicants disagree. Applicant has addressed each statement by the Examiner from the prior art which was put forth to support this conclusion of lack of predictability. There is no evidence of unpredictability of the invention. The variability observed with CpG oligonucleotides is not sufficient to demonstrate unpredictability. It simply shows that some oligonucleotides work better than others at stimulating the immune response. Applicants have identified the key structural property , the unmethylated CpG dinucleotide, that allows this class of oligonucleotides to function through TLR9 to stimulate an immune response that is useful in the treatment of bacterial infection.

Quantity of experimentation necessary:

The Examiner has provided several reasons for why additional experimentation would be necessary. For instance it is stated in the Office Action that "Applicant has not provided any guidance relating to how the immunostimulatory activities observed for several oligonucleotides containing CpG motif translates to the treatment of bacterial infections...pertaining to the type of activity that would need to be stimulated to provide effective treatment against bacterial infections....relating to the level of immune stimulation that would be required to provide effective treatment against bacterial infections." It is unclear how any of these factors relate to extensive experimentation. Applicants have

taught how to make the CpG ODNs using routine methods known in the art. Applicants have also taught that they produce a pattern of immune stimulation and that they can be administered for the treatment of bacterial infection. One of skill in the art would simply need to make the ODN or buy it and administer it to a subject having a bacterial infection. The skilled artisan would know the best routes of administration to use depending on the infectious agent and the subject.

In view of the teaching of the instant application and the state of the art at the time of filing, Applicants submit that the claimed invention can be practiced without undue experimentation. Applicants have provided CpG oligonucleotide sequences that stimulate an immune response (and demonstrated a number of immune parameters *in vivo* and *in vitro*) and have provided guidance to one of ordinary skill in the art to use the CpG oligonucleotides to treat or prevent a bacterial infection. Based on the teachings in the specification one skilled in the art would have predicted that CpG is capable of treating bacterial infection. Numerous references, including those cited by the Examiner, have shown that CpG oligonucleotides can overcome infection, suggesting that CpG ODN is effective in treating bacterial infection. Therefore, the amount of experimentation required to practice the invention is not undue.

Additionally, Applicants enclose herewith copies of several references demonstrating the positive effect of CpG oligonucleotides in the treatment of bacterial infection (listed on attached IDS and including Cellular Microbiology 2003 5(12) 913-920, Diseases of Aquatic Organisms 2003 56(1) 43-48, Immunity 1999 11 123-129, Infection and Immunity 1999 67(11) 5658-5663, Infection and Immunity 2000 68(5) 2948-2953, Infection and Immunity 2001 69(10) 6156-6164, Infection and Immunity 2002 70(1) 147-152, Infection and Immunity 2003 71(2) 857-863, Infection and Immunity 2003 71(12) 7014-7022, Journal of Immunology 1998 161(5) 2428-2434, Journal of Immunology 1999 162 2291-2298, Journal of Immunology 2000 165(8) 4537-4543, Journal of Immunology 2001 167(6) 3324-3328, Springer Semin Immunopathol 2000 22(1-2) 173-183.). The post-filing references are not cited in order to enable the claims but to rebut the rejection that the

post-filing references cited by the Examiner as being sufficient to demonstrate the unpredictability of the claimed invention.

Accordingly, withdrawal of the rejection of claims 42-58, 65, 87 and 96 under 35 U.S.C. § 112, first paragraph is respectfully requested.

Double Patenting Rejection

Claim 104 was provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 19 of copending application No. 10/613619. The rejection is a provisional one since none of the claims in the 10/613619 application has been found allowable. Applicants defer substantive rebuttal until the above-identified claims are allowed.

Claim 104 was provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 67 of copending application No. 10/224523. The rejection is a provisional one since none of the claims in the 10/224523 application has been found allowable. Applicants defer substantive rebuttal until the above-identified claims are allowed.

Claim 104 was provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 38 of copending application No. 10/787737. The rejection is a provisional one since none of the claims in the 10/787737 application has been found allowable. Applicants defer substantive rebuttal until the above-identified claims are allowed.

Claim 104 was provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 30 of copending application No. 10/735592. The rejection is a provisional one since none of the claims in the 10/735592 application has been found allowable. Applicants defer substantive rebuttal until the above-identified claims are allowed.

Claim 104 was provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 41 of copending

application No. 10/894682. The rejection is a provisional one since none of the claims in the 10/894682 application has been found allowable. Applicants defer substantive rebuttal until the above-identified claims are allowed.

Claims Free of Art

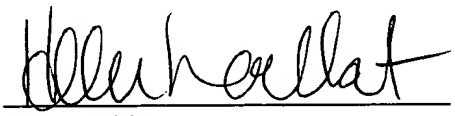
Applicants acknowledge that pending claims 90, 93, 96, 98-101, 133-146, and 149-151 are novel and non-obvious in view of the prior art of record based on the lack of a rejection of those claims.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

Dated: September 27, 2006

Respectfully submitted,

By: 

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